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THE EFFECT OF GINKGO BILOBA AGAINST OTOTOXIC HEARING LOSS ON ADVANCED STAGE UNDIFFERENTIATED NASOPHARYNGEAL CARCINOMA RECEIVING CISPLATIN CHEMOTHERAPY

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Abstract

Introduction: Undifferentiated nasopharyngeal carcinoma is the most common malignant tumor in nasopharynx, in which most patients come to a hospital in advanced stage. Cisplatin is one of the most effective widely used chemotherapy drugs for advanced stage undifferentiated nasopharyngeal carcinoma. Although it provides a successful outcome against cancer, there is serious side effect namely ototoxic hearing loss. Ginkgo biloba is a powerful antioxidant which may prevent ototoxic hearing loss.
Objective: The study aims to determine the effect of ginkgo biloba against ototoxic hearing loss on advanced stage undifferentiated nasopharyngeal carcinoma receiving cisplatin chemotherapy.
Methods: This study was double blind Randomized Control Trial with pre-post test design, was conducted in 22 patients with advanced stage undifferentiated nasopharyngeal carcinoma receiving cisplatin chemotherapy at the Department of Otorhinolaryngology Head and Neck Surgery dr. Moewardi Hospital Surakarta between June 1st and October 1st 2019. The subjects were allocated into control (plasebo) and treatment (80 mg Ginkgo biloba extract) groups. Hearing function was examined with pure tone audiometry, tympanometry and Distortion Product Otoacoustic Emission before and after the first, the second and the third cisplatin chemotherapy. The results of the examination of the two groups were tested using Friedman and Chi Square test. P value of <0.05 was considered significant.
Results: The study subjects were mostly male (63.6%), with the age range of 40-59 years (90.9%). The baseline characteristics of the study subjects were homogeneous (p>0.05). There was a significant difference in the incidence of ototoxic hearing loss between control and treatment group after getting the second and the third chemotherapy (p=0.043 and p=0.033, respectively).
Conclusion: There is a significant effect of ginkgo biloba in term of preventing ototoxic hearing loss on advanced stage undifferentiated nasopharyngeal carcinoma patients receiving cisplatin chemotherapy.

Article Info

Keywords:
Ginkgo biloba; ototoxic hearing loss; nasopharyngeal carcinoma; cisplatin

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1. INTRODUCTION

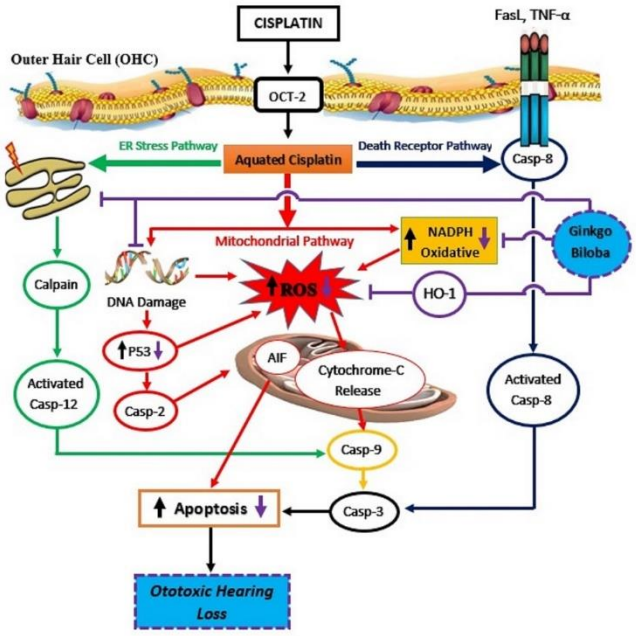
Nasopharyngeal carcinoma (NPC) is a malignant tumor derived from epithelial/ mucosal lining the surface of the nasopharynx, which remains a problem in medicine field. Nasopharyngeal carcinoma is the most common malignancy in Ear Nose and Throat (ENT) cancer it ranks the fourth highest among all types of malignancies. Nowadays it has been reported that the prevalence of NPC in Indonesia is 6.2 per 100.000 population annually[1]. Based on medical records of dr.Moewardi Hospital Surakarta between 2012 and 2014 there were 298 new cases of nasopharyngeal carcinoma in ENT Oncology [2].

WHO classifies NPC into three criteria based on cell differentiation, namely type 1 (keratinized squamous cell carcinoma), type 2 (non-keratinized carcinoma), and type 3 (poorly differentiated/ undifferentiated carcinoma). WHO type 3 occupies the highest percentage compared to two others [1,3].

The early symptoms of NPC are atypical, and some have no symptoms, so that most patients come to the hospital with an advanced stage (stage III or IV). The majority of advanced stage undifferentiated NPC patients receive radiotherapy and chemotherapy[3,4]. Cisplatin is one of the most effective widely used chemotherapy drugs for advanced stages undifferentiated NPC [5,6]. Although cisplatin provides a successful outcome against cancer, it has serious side effects, one of them is ototoxic hearing loss. The ototoxic effect of cisplatin is bilateral sensorineural hearing loss, which is progressively irreversible, started from 6000-8000 Hz frequencies that eventually and will continue to decline if the therapy is continued and it is accompanied by tinnitus [7]. Previous studies reported that the incidence of cisplatin ototoxicity is between 75 and 100% depending on the age, the dose and the number of cisplatin chemotherapy cycles [8].

Early detection of hearing disorder due to drug ototoxicity is very important so that we can change the dose, the drug or prescribe antioxidant in order to avoid more severe sensorineural hearing loss [6,7,9].

Ginkgo biloba is a powerful antioxidant, which contains extracts of ginkgo biloba (EGb 761) 24% flavone glycosides, 6% terpene lactones, and 7% proanthocyaniclines. Flavone glycosides and terpene lactones play pivotal role in inhibiting free radicals, so that oxidative stress and apoptosis of the cells can be prevented [6,7,10]. As antioxidants, ginkgo biloba 761 extract has proven otoprotective to ototoxicity caused by cisplatin examined with Distortion Product Otoacoustic Emission (DPOAE) examination [11,12].



Picture 1. The mechanism of ginkgo biloba in preventing ototoxic hearing loss of cisplatin

Ginkgo biloba inhibits Cisplatin-induced Reactive Oxygen Species (ROS) elevation by hindering oxidative nicotinamide adenine dinucleotide phosphate (NADPH) formation. In addition, ginkgo biloba also prevents endoplasmic reticulum stress and DNA damage, so that caspase-12 and P53 decrease. By inhibiting the endoplasmic reticulum stress, DNA damage and increased ROS, ginkgo biloba reduces apoptosis process of outer hair cells (OHC), so hearing loss will not occur (Picture 1).

The increasing incidence of ototoxic hearing loss in patients with advanced stage undifferentiated NPC receiving cisplatin chemotherapy, encouraged the author to seek additional therapy by using Ginkgo biloba to prevent or to abate ototoxic hearing loss, without attenuating the efficacy of cisplatin in chemotherapy. Hence the patients can have good quality of life by having good hearing function.

2. MATERIAL AND METHODS

This research is an double-blind randomized controlled trial (RCT) with pre-post test design, was conducted at ENT department of dr.Moewardi Hospital Surakarta between June 1st and October 1st 2019. The subjects were 22 patients with advanced stage undifferentiated NPC that receiving cisplatin and fulfilling inclusion and exclusion criteria. The inclusion criteria were patients aged 18-59 years, never received ginkgo biloba or other antioxidants, and willing to join the study by signing the informed consent. Patients with the history of chemotherapy and radiotherapy, received other ototoxic therapy, had perforation of tympanic membrane, sensorineural hearing loss before chemotherapy, renal failure, hepatic insufficiency, and or work in the noisy area were excluded from this study.

Subjects were randomly assigned into two groups, control and treatment groups by using simple Microsoft Excel. The control group receive chemotherapy cisplatin-paclitaxel with additional therapy placebo 1 tablet per day, while the treatment group receive chemotherapy cisplatin-paclitaxel with additional therapy ginkgo biloba 80 mg per day orally. This additional therapy was given 1 day before chemotherapy for 45 days. Hearing examination was performed with pure tone audiometry, tympanometry, and DPOAE before and after the first, the second and the third cisplatin chemotherapy.

Non parametric statistical data were analyzed with Friedman test. The categorical data were analyzed with Chi Square and Fisher Exact Tests. The p value of <0.05 was considered significant.

This study was approved by the Research Ethics Committee, Faculty of Medicine, Sebelas Maret University/ dr.Moewardi Hospital Surakarta by issuing of ethical clearance documents (Ethical Approval Number: 760/VI/HREC/2019).

3. RESULT

During the study period, we found 22 advanced stage undifferentiated NPC patients who fulfilled our inclusion criteria. These subjects were randomly assigned into control (n=11) and treatment (n=11) groups. The baseline characteristic of both groups were homogenous. Thus there were no significant differences between the two groups (p>0.05) (Table 1).

Table 1. Baseline Characteristics of Research Subjects

Characteristics	Control n (%)	Treatment n (%)	p
Sex			
Male	7 (63.6)	7 (63.6)	1,000*)
Female	4 (36.4)	4 (36.4)	
Age			
18-39 y.o	2 (18.2)	0 (0)	0.098**)
40-59 y.o	9 (81.8)	11 (100)	
Mean ± SD	49.09 ± 8.81	54.27 ± 4.52	
Profession			
Labor	2 (18.2)	2 (18.2)	0.639*)
Housewives	3 (27.3)	2 (18.2)	
Trader	4 (36.3)	2 (18.2)	
Retired	0 (0)	1 (9.1)	
Farmer	2 (18.2)	4 (36.3)	
NPC Stage			
III	3 (27.3)	1 (9.1)	0.726*)
IVa	2 (18.2)	2 (18.2)	
IVb	2 (18.2)	3 (27.3)	
IVc	4 (36.3)	5 (45.4)	
Cisplatin Dose			
80-120 mg	11 (100)	9 (81.8)	0.476*)
>120 mg	0 (0)	2 (18.2)	

Note: *) Fisher Exact Test

**) Independent Sample t-Test

Table 1 explains that the gender of the both subjects groups were mostly male, with jobs as traders or farmers. Research subjects who came to the hospital were mostly have stage IVc, and received a dose of cisplatin chemotherapy is 80-120 mg. Then the Fisher Exact test was performed with a result of p>0.05 which means that there was no significant relationship between the control group and the treatment group, or the characteristics of the study subjects were homogeneous.

The research subjects in the control group were mostly 40-59 years old (81.8%), while in the treatment group all the study subjects were 40-59 years old (100%). Shapiro-will test was performed to determine the normality of data distribution, with the results of p=0.62 (p>0.05) which means the data is normally distributed. Then the statistical analysis test was performed with an independent sample t-test to determine whether there were differences in the mean age in the control and treatment groups, the results were p=0.98 (p>0.05) which meant there were no significant differences, so the subjects of this study were homogeneous.

Table 2. Tympanometry Examination Results

	Tympanometry Results	Control n (%)	Treatment n (%)	P*
Right ear				
	Type A	2 (18.2)	3 (27.3)	1.000
	Type B	9 (81.8)	8 (72.7)	
Left ear				
	Type A	2 (18.2)	3 (27.3)	1.000
	Type B	9 (81.8)	8 (72.7)	

Note: * Fisher Exact Test

Tympanometry examination performed in the control and the treatment groups obtained no significant differences between the two groups (p=1.000). Tympanometry results in both groups were mostly type B for the left and the right ears (Table 2).

Table 3. The Results of DPOAE Examination

DPOAE (REFER)	Control n (%)	Treatment n (%)	p
Pre Chemo	0 (0)	0 (0)	-
Post Chemo 1	3 (27.3)	0 (0)	0.214*)
Post Chemo 2	7 (63.4)	1 (9.1)	0.024*)
Post Chemo 3	9 (81.8)	3 (27.3)	0.010**)

Note: *) Fisher Exact Test

**) Chi Square Test

None of the subjects in both groups undergoing DPOAE examination before chemotherapy had "REFER". Post first cisplatin chemotherapy 3 subjects in control group had "REFER" and none in treatment group (p=0.214). This finding (REFER) increased in both groups in post chemotherapy 2 and 3, they were 7 and 9 in control group and 1 and 3 in treatment group (p=0.024 and p=0.010, respectively) (Table 3).

The significant differences between the two groups were observed started at post second chemotherapy. More subjects in control group had DPOAE finding of REFER than those in treatment group.

Table 4. Ototoxic Hearing Loss Control Group and Treatment Group

Ototoxic Hearing Loss	Control n (%)	Treatment n (%)	p
Pre Chemo	0 (0)	0 (0)	-
Post Chemo 1	3 (27.3)	0 (0)	0.214[a]
Post Chemo 2	6 (54.5)	1 (9.1)	0.043[a]
Post Chemo 3	8 (72.7)	3 (27.3)	0.033[b]

Note: [a] Fisher Exact Test

[b] Chi Square Test

Based on American Speech-Language Hearing Association (ASHA) criteria we found more subjects with ototoxic hearing loss in control group than those in treatment group. Statistical test results of both groups show p value of 0.214 (p>0.05) for the first cisplatin chemotherapy, which means there was no difference significant incidence of ototoxic hearing loss on control and treatment group. The second and third post-chemotherapy obtained p value of 0.043 and 0.033 (p<0.05), showed a difference significant incidence of ototoxic hearing loss on control and treatment group (Table 4).

4. DISCUSSION

In our study we analyzed the incidence of ototoxic hearing loss before and after cisplatin chemotherapy in patients with advanced stage undifferentiated NPC. These patients were randomly assigned into control and treatment groups. For the control group we gave cisplatin-paclitaxel only while the treatment group we administered cisplatin-paclitaxel plus ginkgo biloba.

Most of our study subjects were male with the age ranged from 40 to 59 years old. This finding is similar to that of Jayalie et al study in Cipto Mangunkusumo Hospital Jakarta. They reported that 68.3% of NPC patients were males and 80.2% were in the age of over 30 years old. Barata as well as Whitehorn et al in 2014 also reported that male was more predominant than female among NPC patients (55% and 73.8%, respectively).

Distortion Product Otoacoustic Emission (DPOAE) is a quick and objective electrophysiologic tool to determine the state and the function of cochlear outer hair cells. It also can detect response at high frequencies. "REFER" in DPOAE examination demonstrates the damaged function of cochlear outer hair cell [7,12].

Our DPOAE examination obtained less "REFER" results in our subjects receiving additional therapy of Ginkgo biloba. This is also an evidence that cisplatin ototoxicity impact hearing function significantly. In our study 81.8% subjects in control group suffered from hearing loss after their third chemotherapy with cisplatin-paclitaxel. Putri et al study also reported that DPOAE can detect early events of cisplatin ototoxicity (100%).

The effect of ototoxic hearing loss can also be detected by pure tone audiometry examination. Based on ASHA criteria it is regarded ototoxic hearing loss if there are one of the three following criteria: 1). Decrease ≥20 dB at least one frequency, 2). Decrease ≥10 dB at least two adjacent frequencies, 3). Loss of response on three successive frequencies that are on previous checks are still responding [13,14].

Pure tone audiometry examination performed in our study subjects demonstrated that the incidence of ototoxic hearing loss was higher in control group than that of in treatment group. This result is similar to that of done with DPOAE examination. Therefore, pure tone audiometry can be recommended for detecting ototoxic hearing loss, especially in patients with advanced stage undifferentiated NPC.

Ginkgo biloba is a powerful antioxidant which plays an important role in preventing ototoxic hearing loss due to cisplatin by inhibiting the formation of free radical [10,15]. In our study, adding ginkgo biloba to cisplatin-paclitaxel can prevent or reduce the incidence of ototoxic hearing loss in patients with advanced stage undifferentiated NPC receiving cisplatin chemotherapy. This is in accordance with the study by Sampaio et al (2016), which reported that ginkgo biloba significantly prevented sensorineural hearing disorders in malignant tumor patients undergoing cisplatin chemotherapy. Dias et al (2015) who conducted a study in cancer patients found a significant decrease in hearing threshold at the frequency of 8 KHz in subjects who did not receive ginkgo biloba as compared to them in treatment group who had ginkgo biloba. Choi et al study also stated that ginkgo biloba extract significantly prevented cochlear outer hair cell damage due to cisplatin and inhibited down regulation of Gap Junctional Intercellular Communication (GJIC). Gap Junctional Intercellular Communication disorders play important role in the mechanism of ototoxic hearing loss induced by cisplatin. It has been proven that ginkgo biloba has proapoptosis activity againts NPC and does not interfere cisplatin anti tumor activity, it also owns no side effect.

5. CONCLUSION

There is a significant effect of ginkgo biloba in term of preventing ototoxic hearing loss on advanced stage undifferentiated NPC patients receiving cisplastin chemotherapy. Ginkgo biloba is safe as it has no side effect. Therefore adding Ginkgo biloba to cisplatin chemotherapy can be benificial for patients with advanced stage undifferentiated NPC so that their quality of life improves since they have good hearing function.

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